European Commission

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EUROPEAN MEDICINES AGENCY

HMA
Heads of Medicines Agencies

ACT EU multi-stakeholder workshop: A patient-centered approach to methodologies

Report of the methodology guidance workshop

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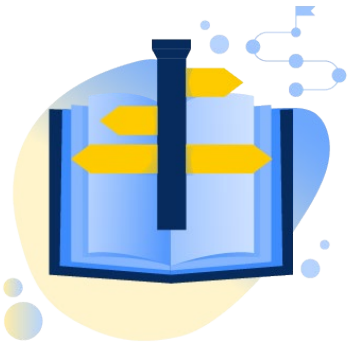
An agency of the European Union

Contents

Executive Summary

The ACT EU multi-stakeholder workshop on methodology guidance facilitated a discussion between relevant stakeholders on key topics of clinical trial methodology. The objective of the workshop was to identify the challenges stakeholders face, propose ways for improving patient centricity and suggest possible solutions. In break-out sessions, participants from relevant stakeholder groups discussed complex clinical trials, paediatric trials, pragmatic trials, digital endpoints, evidence generated in non-randomised designs, patient centricity, decentralised trials, and platform trials.



The following key themes emerged across the different break-out sessions.

Challenges

- The multitude of guidance documents and requirements from a variety of stakeholders makes it difficult to plan a trial that is acceptable to all decision-makers.
- With the In Vitro Diagnostic Regulation, Medical Device Regulation and Pharma Legislation, multiple legislative frameworks apply within the EU that are difficult to navigate.
- Requirements of the Clinical Trial Regulation are new and implementation may differ across EU member states.
- Evidentiary requirements for decision-making are not always clear.
- Patient communities are often not aware of relevant planned and ongoing clinical trials.

Improving patient-centricity

- Consult patients and practitioners consistently and early on during the design and conduct of clinical trials and the development of guidance on clinical trial methodology.
- Provide easily accessible and understandable information about the clinical trial for participants.
- Ensure adequate compensation for patient input into clinical trial design.
- Improve the visibility of clinical trials.

Solutions

- Clarify regulatory requirements by developing new guidance or updating existing guidance.
- Improve the alignment between Regulatory Agencies, Health Technology Assessment bodies and Notified bodies within Europe and aim to harmonise regulatory requirements internationally.

- Clarify requirements of the Clinical Trial Regulation and strive for alignment between EU Member States.
- Reduce the bureaucratic burden for trial conduct and improve processes and IT systems for clinical trial registration.
- Increase clarity and consistent use of existing regulatory pathways.
- Improve pre-competitive collaboration of stakeholders and data sharing.

The discussions also highlighted the topics that would benefit from further clarification, by developing new guidance or updating existing guidance:

- The definition of "normal clinical practice" to facilitate treatment optimisation trials with already approved medicinal products.
- The definition of "unmet medical need".
- Age-inclusive research and including paediatric patients into adult clinical trials.
- The recommendation paper on Ethical considerations for clinical trials conducted with minors.
- Drug development for neonates.
- Conducting clinical trials in small populations with a specific focus on N of 1 clinical trials.
- Evidentiary requirements for the qualification of digital endpoints for use in clinical trials.
- Systematically guiding the dialogue between sponsors, regulatory bodies (National Competent Authorities and Ethic committees) and Health Technology Assessment bodies on the acceptability of non-RCT designs.
- The operationalisation of the Clinical Trial Regulation requirement describing patient involvement in clinical trial designs.
- The regulatory acceptability of methodological aspects of platform trials.

As next steps, focussed follow-up discussions and further workshops will be needed to consider the outcomes from the break-out sessions. The workshop report will be disseminated publicly and presented to relevant expert groups in the European Medicines Regulatory Network to acknowledge the challenges identified by all stakeholders and to consider the proposed ways for improving patient centricity and addressing the stakeholder challenges.

Introduction

Opening remarks by Emer Cooke (EMA), Karl Broich (HMA), Isabelle Clamou (European Commission) and Workshop Chairs Monique Al (CTCG) & Kit Roes (MWP)

Excellent clinical trials are core to the generation of high-quality clinical evidence benefitting patients and healthcare in Europe. Accelerating Clinical Trials in the EU (ACT EU) is a joint initiative of the European Commission, Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) that supports clinical trials conducted in Europe through regulatory, technological and process innovation.

The evolving clinical trials landscape is an opportunity to improve coordination between stakeholders, regulators and ethics committees, aiming for clinical trials that meet the needs of all involved stakeholders, and particularly benefit patients and healthcare in the EU.

To ensure that clinical trials generate fit-for-purpose evidence, the European Medicines Regulatory Network provides guidance on clinical trial methodology, supporting trial sponsors in the implementation of new and innovative approaches for the design and conduct of clinical trials. Therefore, the development of guidance on clinical trial methodologies is among the ACT EU priority areas. As part of this work, ACT EU has already supported the publication of a Q&A document on complex clinical trials and a recommendation paper on decentralised clinical trials.

The ACT EU multi-stakeholder workshop on methodology guidance invited early input from all relevant stakeholders on key methodology topics, selected based on a public call for topics. A Break-out session was dedicated to each selected topic. Participating experts discussed challenges and needs around clinical trial methodology guidance, while keeping patients' needs at the centre of discussions. Participants also discussed possible ways for the European Medicines Regulatory Network to address the identified challenges and for improving patient centricity and involvement. These discussions will inform the future development of guidance by the European Medicines Regulatory Network.

Session A

Complex trials I

Moderators: Olga Kholmanskikh (FAMHP), Frank Petavy (EMA)

Presenters: Olga Kholmanskikh (FAMHP), Laura Arenare (Istituto Nazionale Tumori IRCCS Fondazione Pascale), Sahar Barjesteh van Waalwijk van Doorn-Khosrovani (CZ Health Insurance, Leiden University Medical Centre), Nicky Best (GSK) and Kaspar Rufibach (Roche)

The session opened with an introduction to the evolving clinical trials ecosystem and to the Q&A document on complex clinical trials followed by a presentation on the concept of Patients' Journey Studies (PJS), where each node of clinical decision-making can be a randomisation if there is equipoise between different options. This type of trial addresses questions regarding subsequent lines of treatment and overall strategies that are generally left unanswered at the time of marketing authorisation.

The Drug Rediscovery Protocol (DRUP) and the DRUP-like trials (the PRIME-ROSE consortium) were presented as examples of multi-drug, pan-cancer precision oncology trials, where the provision of treatments to patients belonging to rare and under-studied subpopulations is combined with data-collection and analysis, from preliminary stages to expansion cohorts. In these trials, successful cohorts will undergo central assessment and groundwork will be established to facilitate Health Technology Assessment (HTA) analysis and reimbursement decisions to ensure equitable access.

The session closed with a presentation on the different estimands of interest for different stakeholders and of the technical and operational problems in pursuing estimation of all those in a development plan, highlighting the need for guidance for the role of augmented control.

Key challenges identified by stakeholders

- There is a trade-off between trying to answer many relevant questions in one trial (which would favour the option of designing complex trials) and interpretability and robustness of trial results (which would favour simpler studies).
- The multitude of guidance documents and requirements from a variety of stakeholders makes it difficult to plan a trial that is acceptable to all decision-makers.
- Assessing the feasibility of trials can also be challenging, given the imperfect knowledge of patients' and prescribers' preferences and the different treatment opportunities outside of trials.

How to improve patient-centricity

- The value of answering all the questions that inform joint decision-making of doctors and patients (including with post-authorisation trials) has to be recognised by all stakeholders, and trials that are suited for this purpose have to be prioritised.
- Patients and practitioners should be increasingly consulted in designing clinical trials; the acceptability of certain designs and the desirability of collecting specific outcome measures should not be assumed, but proactively discussed and supported with data.

Suggested ways forward to address the challenges

- Methodological research on the risk of false positive conclusions (especially at a regulatory decision level) and the potential of bias in different types of complex trials, as well as on possible mitigation strategies, has to be prioritised.

- Guidance should be developed with increasing degrees of harmonisation between different decision-makers (clinical trial approval bodies, marketing authorisation bodies, HTA bodies, prescribers), so that trials that satisfy the requirements of all are increasingly enabled.
- Post-authorisation clinical trials (of the type of DRUG-Access Protocol and PJS) – including by academic sponsors - that aim at addressing questions that go beyond the requirements of marketing authorisation have to be promoted. As these trials often require complex designs, provision of robust guidance is important.

Session B

Paediatric trials

Moderators: Anette Solli Karlsen (Norwegian Medicines Agency) and Dina Apele-Freimane (State agency of Medicines of Latvia)

The session focused on paediatric trials as part of the drug development and related methodology guidance needs. The changes in requirements for paediatric clinical trials brought about with the implementation of the Clinical Trial Regulation (CTR) and the need to revise the recommendations on ethical considerations for clinical trials with minors were presented. Academic studies investigating treatment optimisation in paediatric oncology were discussed, providing the view of clinicians on the interrelation between the Clinical Trial Directive (CTD) and CTR and these academic studies. The industry perspective on the current situation for paediatric clinical trials was also presented, focusing on opportunities for optimisation and highlighting the value of public-private partnerships. The session highlighted the importance of patient involvement from the conception and design phase to address the challenges in paediatric clinical trials.

Key challenges identified by stakeholders

- Paediatric drug development is mostly conducted in global drug development programs with diverse regional guidelines which need to be adhered to.
- Terminology lacks a clear definition and is used heterogeneously, for example, the terms "normal clinical practice" and "unmet medical need".
- Paediatric clinical trials are often conducted for overlapping patient populations, also in relation to adult trials, which creates a barrier to the conduct based on small populations.
- Paediatric patients and/or their parents/caregivers are rarely included in the planning, conduct and reporting of paediatric clinical trials.
- Age-inclusive research is important for faster knowledge on the best treatment as well as timely access for the paediatric population, but is challenging with no guidance on when it is acceptable.
- The CTR requirement for paediatric clinical trials to have direct benefit for the individual taking part in the trial has not been implemented in a harmonised manner at national level.
- In small populations randomised clinical trials (RCTs) are most often not feasible; in such cases, data collection from N of 1 trials may be considered as a solution. There is lack of guidance and understanding, however, on how such trials should be conducted and fit within the regulatory system.
- Some diseases occur in neonates-only, but dedicated guidance on trials in this special population is lacking.

How to improve patient-centricity

Paediatric patients and/or their parents/caregivers should be involved in the conception and design of clinical trials to ensure the relevance of the design elements for paediatric patients and to increase feasibility from a recruitment and adherence standpoint.

- Diversity needs to be considered when designing patient and public involvement in clinical trials aiming to represent all relevant groups affected by the disease studied in these trials.

- Documentation of patient involvement during the drug development process, including the design of clinical trials, should be part of a clinical trial application. Regulators should request information about patient involvement.
- Patient and public involvement activities need to be led by paediatric experts to ensure the quality of the methods and outcomes, the protection of children's rights and ethical principles, and to avoid any kind of conflict of interest or bias in the process.
- In paediatric clinical trials, patient involvement should be interpreted to include family members and other caretakers.

Suggested ways forward to address the challenges

Key general points to consider when writing guidance for paediatric clinical trials are:

- Guidance should not be developed in isolation in one regulatory region but rather be cross-regional, if possible, to ensure equal opportunities for patients around the world.
- When methodology guidance is developed, special attention should be given to aspects which might be different for a paediatric population.
- Multi-stakeholder collaboration is necessary when developing guidance.

Suggestions for development/updating of guidance:

- Clarify the definitions of "normal clinical practice" to facilitate treatment optimisation trials with already approved medicinal products. It is recommended that clinical medical societies should drive the definition of this term.
- Clarify the definition of "unmet medical need".
- Develop guidance on when and how age inclusive research, including paediatric patients into adult clinical trials, is acceptable.
- Update the recommendation paper on Ethical considerations for clinical trials on medicinal products conducted with minors from the Commission as published on Eudralex volume 10.
- Clarify the CTR requirement for paediatric clinical trials to have direct benefit for the individual taking part in the trial, and the expectation for medical conditions that occur in minors and adults, but which manifest themselves in a different way at a young age. Harmonisation is needed between EU members state views, including that of the ethics committees.
- Develop guidance on drug development for neonates.
- Update the EMA guidance on how to conduct clinical trials in small populations with a specific focus on N of 1 clinical trials.
- Ensure consistent use of terminology on extrapolation in the context of paediatric drug development when methodology guidance is updated.

Session C

Pragmatic trials

Moderators: Frederik Grell Noergaard (DKMA), Claire Bahans (Research Ethics committees, FR)

Presenters: Beate Wiesler (IQWiQ), Rudolf Huber (Ludwig-Maximilians-Universität Munich), Denis Lacombe (EORTC), Nafsika Kronidou Horst (Roche).

The benefits of pragmatic trials to provide data on comparative effectiveness in routine care were presented, noting that randomisation is a key element for HTA. The session also explored the role of pragmatic trials in generating relevant data, optimising treatment and informing routine clinical practice. The value of pragmatic trials for patients, clinicians and payers was underlined, as these trials combine the methodological strengths of RCTs with the inclusiveness of a real-world setting. Pragmatic trials were highlighted as key to optimising the appropriate use of medicinal products and, for example, adjusting dose and schedule notably in de-escalation trials. The EFPIA position paper on randomised pragmatic trials to inform regulatory decisions was presented, focusing on the key considerations, learning opportunities and possible regulatory settings for the use of such trials.

Key challenges identified by stakeholders

- Randomised pragmatic trials are often conducted by non-commercial sponsors, where the burden to comply with the CTR is too resource-consuming rendering the trials unfeasible. The main challenges are the workload for reporting of safety events with lack of clarity on the low interventional clinical trial borderline and the requirements for reimbursement of investigational medicinal products.
- The relevance of research questions and outcomes can differ according to stakeholders' points of view (e.g. patients, HTA bodies, National Competent Authorities (NCAs), Ethics Committees) and across Member States, e.g. in regard to the choice for "standard of care" and "clinical practice''.
- The definition of pragmatic trials is not clear with partial overlap with other study types such as trials with decentralised elements.

How to improve patient-centricity

- Patients should be involved from the beginning of research conception and design. Treatment optimisation and quality of life are key points for patients, together with the reduction of operational complexities e.g. lengthy and complex informed consent.
- The trial summary for patients in a pragmatic trial should be simplified.

Suggested ways forward to address the challenges

- Reduce the bureaucratic burden for pragmatic trials e.g. with a risk-based approach regarding safety registration and reporting, in line with ICH E19 and the CTR. Initiatives should include sponsors, patients and practitioners and focus on simplifying trial protocols.
- Ensure that the design of clinical trials can provide data suitable for marketing authorisation and reimbursement decisions. To this point, joined scientific advice including HTA and ethics could be explored.
- Designing clinical trials with more pragmatic elements during medicines development could reduce the need for additional trials/evidence after drug approval.

Session D

Digital Endpoints

Moderators: Jesper Kjaer (DKMA), Thorsten Vetter (EMA)

Presenters: Martin Daumer (School of Computation, Information and Technology), Lada Leyens (Takeda), Laurent Servais (Oxford University)

The session opened with presentations on the development and validation of digital endpoints from an academic perspective, followed by the EFPIA perspective on opportunities and challenges in validating digital endpoints. Lastly, experience with the EMA qualification procedure for the "Stride velocity 95th centile" (SV95c) as a qualified primary endpoint for studies in Duchenne Muscular Dystrophy was presented.

Key challenges identified by stakeholders

- It is difficult for a single developer to generate sufficient high-quality data needed for the development, validation and qualification of digital endpoints.
- With the (IVDR), Medical Device Regulation (MDR) and Pharma Legislation, multiple regulatory frameworks apply within the EU that are difficult to navigate and are not always aligned. Furthermore, there is a lack of international harmonisation.
- Evidentiary requirements for validating and qualifying digital endpoints are not clear.
- Including (too) many measures to generate evidence for the development and validation of new (digital) endpoints in a clinical trial puts burden on patients, challenging patient retention and trial conduct.

How to improve patient-centricity

- Involvement of patients from the earliest stages in the development of new endpoints and digital measures is key to ensure relevance and practicality.
- Ensure proportionality in generating data for the development and validation of a new endpoint in a clinical trial, balancing the burden of the patients participating in the trial with the benefit of developing a new relevant endpoint.

Suggested ways forward to address the challenges

- Build on the experience of the CHMP Qualification Opinion for a digital endpoint in Duchenne Muscular Dystrophy (SV95c), as well as other examples, regarding evidentiary requirements and processes as well as scientific and technical learnings in the development of digital endpoints in related diseases.
- Stakeholders should engage in early regulatory dialogue using the available support platforms: EMA support to SMEs, EMA Innovation Task Force briefing meetings, EMA Scientific Advice for product specific methodology development, EMA Qualification of Novel Methodologies.
- To accelerate the development and validation of digital endpoints in a learning eco-system, the pre-competitive collaboration of stakeholders needs to be increased, including data sharing by clinical trial sponsors and secondary use of clinical trial data. Therefore, it is important to make optimal use of public-private partnerships and support the development of novel pre-competitive collaboration frameworks for the development, validation and qualification of

digital endpoints that encourage the translation of new technology into clinical research in practice.

- Improve the alignment between Regulatory Agencies, HTA bodies and Notified bodies within Europe and harmonise regulatory requirements internationally.
- Increase the clarity of existing regulatory pathways for digital endpoint qualification and consider process improvements, in particular on the need for Digital Health Technologies to be certified as medical devices by Notified Bodies based on the MDR/IVDR and documents needed for clinical trial applications.
- Provide guidance on the evidentiary requirements for the qualification of digital endpoints for use in clinical trials.

Session E

Beyond RCTs

Moderators: Elke Stahl (BfArM), Antoine Vanier (HTA, HAS France); Frank Petavy (EMA)

Presenters: Mouna Akacha (Novartis), Denis Lacombe (EORTC), Pierre Henri Bertoye and Claire Bahans (EC France) and Antoine Vanier (HTA, HAS France)

The session opened with the industry perspective on clinical trial methodology beyond RCTs, followed by an ethics view and an academic perspective on synthetic and external controls for clinical trials. The introduction concluded with an HTA perspective on non-randomised studies as source of clinical evidence.

Key challenges identified by stakeholders

- Non-RCT designs are generally associated with an increased risk of bias and reduced confidence in the reliability of results.
- Non-RCT designs are generally associated with higher methodological complexities, such that a strengthened dialogue between decision-making entities could be beneficial.
- A critical consideration for the acceptability of non-RCT designs is the need for strong knowledge about the counterfactual (i.e., what the clinical outcome would have been, had a patient not taken the treatment), which is a challenge in almost all therapeutic indications.
- Experience and knowledge are constantly evolving, which complicates the specification acceptance criteria for non-randomised designs.
- Optimised use of the accumulated knowledge is impeded by the limited sharing of data across stakeholders.
- Stakeholders expressed uncertainty regarding the required level of evidence across decision-making entities, and in which situations non-RCT designs could be considered acceptable. A challenge which was acknowledged in this regard was that the amount of information which can be presented to decision-makers will evolve over time.

How to improve patient-centricity

- When developing a methodological framework to guide the dialogue on the acceptability of non-RCT designs, include considerations related to the specific target indication (such as medical knowledge about the counterfactual).
- Foster and facilitate the conduct of multi-national trials for overcoming perceived obstacles of trials conducted in small patient populations.

Suggested ways forward to address the challenges

- Develop a framework to systematically guide the dialogue between sponsors, regulatory bodies (NCAs and Ethics) and HTAs on the acceptability of non-RCT designs.
- Foster enhanced collaboration and data sharing across stakeholders for optimised use of accumulated medical knowledge.

Session F

Patient-centricity, diversity and representativeness in clinical trials

Moderators: Anneliene Jonker (World Duchenne Organization / UPPMD) and Mårten Wendt (CTCG)

Presenters: Louise Veltrop-Duits (Central Committee on Research involving Human Subject (CCMO)), Tarec Christoffer El-Galaly (Aalborg University Hospital and Danish Medical Research Ethics Committees), Mireille Muller (Novartis) and Michal Rataj (European Patients Forum).

The session opened with an introduction to patient engagement and its importance. The second presentation on Diversity and inclusion in clinical trials focused on scientific needs and ethical obligations. This was followed by a presentation of an industry perspective on methodological priorities on patient centricity, inclusion and representativeness and, lastly, some proposals for making research more patient-driven.

Key challenges identified by stakeholders

- Unclear expectations about clinical trial participation can lead to dropout during trial conduct and follow-up.
- From a patient perspective, potential clinical trials are difficult to identify, reducing the accessibility of trials.
- Trial results are rarely communicated in a timely manner to participants, or it is difficult for patients to locate them.

How to improve patient-centricity

- Patient-centricity should be a general guiding principle in the design and conduct of clinical trials.
- Patients should be involved early on in the design of clinical trials.

Suggested ways forward to address the challenges

- Develop guidance on the operationalisation of the CTR requirement describing patient involvement in clinical trial designs.
- Use Real-World Evidence to complement insights from clinical trials.
- Ensure that patients are adequately compensated for their time and input into clinical trial design and methodology.
- Clarify inclusion and exclusion criteria and their rationale in clinical trials.
- Align on terminologies, especially on diversity and representativeness in clinical trials.
- Increase clarity on expectations of trial participation by providing adequate information to patients.

Session G

Decentralised elements in clinical trials

Moderators: Monique Al (CTCG), Wolfgang Berdel (Association of Medical Ethics Committees, DE)

Presenters: Christine Dehn (German Heart Foundation), Mira Zuidgeest (University Medical Center Utrecht), Alison Bond (Amgen), David Wright (AstraZeneca)

The session opened with a patient perspective on use of decentralised elements in clinical trials (DCTs), emphasising that the main barrier to successful trial conduct is awareness of the trials with decentralised elements. An academic perspective on DCTs was then presented, promoting a change in perspective from the site-based approach as the 'gold standard' to the use of decentralised elements as a normal approach in clinical trials. The perspective from EFPIA emphasised the lack of harmonisation across Member States and the lack of clarity on acceptability and validation of digital/remote endpoints as the key challenges.

Key challenges identified by stakeholders

- Despite the enthusiasm, clinical trial applications with decentralised elements are still sparse. There is uncertainty on the regulatory acceptability of data generated by DCTs for marketing authorisation.
- Awareness of planned and ongoing DCTs among patients is lacking. It is a major challenge to inform patients about the possibilities to take part in a DCT, which is not being conducted by the already treating physician.

How to improve patient-centricity

- Introduce flexibility for patients to participate onsite or remotely may improve the possibilities for patients to participate in trials but may also pose operational and statistical challenges. Clear guidance on how to mitigate the additional challenges can help to realise the benefits of decentralised trial elements for patients.
- Ensure reimbursement for trial related tests and/or services not performed onsite but with local health care providers.
- Implement adequate procedures to ensure equal importance of patients using decentralised and centralised elements.

Suggested ways forward to address the challenges

- More clarity on and faster validation of digital/remote endpoints.
- Increase awareness among investigators and patients on the concept of decentralised elements in clinical trials and explore better use of the local health care practitioners in the conduct of clinical trials.
- More case studies/examples are needed to develop best practices and facilitate harmonisation of requirements across Member States. Ongoing data and knowledge exchange between Member States from applications on DCT elements is important.
- Increase awareness of the existing recommendations published by the EMRN: "Recommendation paper on Decentralised elements in Clinical Trials".

Session H

Complex trials II

Moderators: Elina Asikanius (FIMEA), Olga Kholmanskikh (FAMHP), Benjamin Hofner (PEI)

Presenters: Saskia Litiere (EORTC), Tobias Mielke (Johnson & Johnson), Beate Wieseler (IQWiG)

The session opened with an introduction to the regulatory activities related to platform trials and summary of the status of the Reflection Paper on platform trials. Thereafter, an academic organisation's perspective on complex clinical trials was presented, covering operational and methodological challenges. The EFPIA perspective on platform trials with a focus on opportunities and challenges, particularly in relation to the EMA concept paper on platform trials followed. Lastly, an HTA perspective was presented on how pre- and post-approval platform trials across different new interventions can facilitate the assessment of relative effectiveness.

Key challenges identified by stakeholders

- Conceptualising and operationalising collaboration and sponsorship in multi-stakeholder platform trials investigating products from different competing developers, who may have differing standard operating procedures and legal requirements.
- Lack of sponsor experience, resulting in perceived higher risk for delays and (operational) study failure for investigational interventions.
- Confidence in regulatory acceptability of various design elements, including:
    - Definition and use of type-I-error in platform trials across study arms.
    - Choice of comparator and use of non-concurrent controls; need for guidance on conditions for acceptability of using non-concurrent controls.
    - Partial unblinding of ongoing trial arms after analysing and publishing information on earlier closed trial arms, which makes information on the shared control arm available while other arms are still ongoing.
    - Definition of the population in a platform trial and impact on the randomisation, e.g. in biomarker-driven designs.
    - Response-adaptive randomisation in platform trials with registrational intent.
- Challenges in initiating and conducting platform trials under the CTR and registration via CTIS:
    - Deciding on the optimal submission strategy, either with a single trial application approach (with the platform trial as a single trial) or a multiple trial application approach (with each sub-protocol as individual trials) and anticipating their consequences.
    - Complexity of using CTIS, especially with a lack of functionalities specific to platform trials.
    - The sequential handling of trial amendments via CTIS and related waiting times conflict with the dynamic addition or modification of sub-studies in platform trials.
    - Transition of previously initiated complex clinical trials to the CTR.

How to improve patient centricity

- Accurate and well-described staged process for informed consent.

- Broad exploration of optimal indication in a targeted development (e.g. exploring various biomarkers or combinations thereof, including biomarker positive and negative patients).
- Early ideation of platform trials within indication(s) to facilitate comparisons for downstream decision-making for HTAs, caregivers and patients, by inclusion of as many of the relevant products developed in the respective disease as possible.

Suggested ways forward to address the challenges

- Collaborative and iterative multi-stakeholder dialogue exploring and defining the requirements for the design of a platform trial and facilitating early information sharing on lessons learned and acceptable design elements between various developers.
- Guidance on the regulatory acceptability of methodological aspects of platform trials, to be read in conjunction with the Q&A on complex clinical trials.
- Sponsors collaborate as co-sponsors or third-party organisations act as sponsors in multi-developer platform trials. Important aspects to consider in this setting are the governance structure of the platform trial, experience of the organisation with conducting complex trials, data sharing, data quality and accountability of the applicant in regulatory submissions.
- Clarifications on clinical trial application, approval and conduct processes and procedures for clinical trials that are considered or labelled 'complex', including functionalities in CTIS.
- Identification of novel pilot cases for platform trials in situations with medical need, limited competitive nature and existent regulatory requirement for the study conduct (e.g. paediatric studies) to generate and share experience in design and conduct of cross-company platform trials.

Closing remarks

Chairs: Monique Al (CTCG), Kit Roes (MWP), Peter Arlett (EMA), Florian Lasch (EMA)

To facilitate better, faster and optimised clinical trials in the EU, clinical trial methodology is essential. Therefore, guidance on clinical trial methodology provided by the European Medicines Regulatory Network facilitates the implementation of innovative approaches.

Patients are at the core of clinical development and successfully incorporating patient's needs and perspectives is key for feasible clinical trials that generate fit-for-purpose evidence.

The ACT EU multi-stakeholder workshop on methodology guidance has brought together experts representing all relevant stakeholders of clinical trials in the EU. In line with ACT EU's vision to increase collaboration and coordination across the EU, key topics related to clinical trial methodologies were discussed from a multi-stakeholder perspective. The discussions identified challenges and needs related to guidance development, as well as proposals for how these can be addressed.

As a next step, focussed follow-up discussions and further workshops will be needed to consider the outcomes from the break-out sessions.

The workshop report will be disseminated publicly and presented to relevant expert groups in the European Medicines Regulatory Network to acknowledge the challenges identified by all stakeholders and to consider the proposed ways for improving patient centricity and addressing the stakeholder challenges for inclusion in their workplans.

Glossary

ACT EU	Accelerating Clinical Trials in the EU
CHMP	Committee for Medicinal Products for Human Use
CTCG	Clinical Trials Coordination Group
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
DCT	Decentralised Clinical Trial
DKMA	Danish Medicines Agency
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
EORCT	European Organisation for Research and Treatment of Cancer
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSPI	European Federation of Statisticians in the Pharmaceutical Industry
FAMHP	Federal Agency for Medicines and Health Products
FIMEA	Finnish Medicines Agency
HMA	Heads of Medicines Agencies
HTA	Health Technology Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IVDR	In Vitro Diagnostic Regulation
MDR	Medical Device Regulation
MS	Member State
MWP	Methodology Working Party
NCA	National Competent Authority
PEI	Paul-Ehrlich-Institut
PJS	Patients' Journey Studies
RCT	Randomised Controlled Trial
SME	Small and Medium-sized Enterprise

More information

The Accelerating Clinical Trials in the EU (ACT EU) initiative aims to develop the European Union further as a competitive centre for innovative clinical research. ACT EU seeks to deliver on the clinical trial innovation recommendations of the European medicines agencies network strategy and the European Commission's Pharmaceutical strategy for Europe.

ACT EU builds on the Clinical Trials Regulation and Clinical Trials Information System launched on 31 January 2022. The European Commission, EMA and Heads of Medicines Agencies launched ACT EU in January 2022 and run the initiative together, establishing a steering group in March 2022. The programme's strategy paper features ten priority action (PA) areas that are the basis for the ACT EU workplan; an eleventh PA on clinical trials in public health emergencies has been created since the launch of the programme.

The ACT EU workplan was published on 10 November 2023 and sets out deliverables and timelines for the programme for 2023-26. The deliverables for 2024 include:

- The **implementation of the Clinical Trials Regulation**, including support for the transition of clinical trials to the CTR and the CTR Collaborate project, which aims to optimise collaboration between national health authorities and national ethics bodies.
- The creation of a regulatory **helpdesk for non-commercial sponsors** conducting multi-national clinical trials.
- Creation of the **Multi-Stakeholder Platform Advisory Group** of stakeholder representatives.
- A **scientific advice pilot** to provide consolidated advice for clinical trial and marketing authorisation applications.
- Regulatory support to **clinical trials in public health emergencies**.

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